Allergy Abstracts

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Asthma and Hay Fever

Continuous Steroid Hormone Treatment of Chronic Asthma. I. Cortisone and Hydrocortisone. MacLaren, W. R., and Frank, D. E.: Ann. Allergy **14**: 183, 1956.

A group of 37 adults and 15 children who had suffered from bronchial asthma and/or neurodermatitis for at least 2 years, and who had failed to respond to other types of therapy, were arbitrarily divided into 3 groups and were treated with cortisone and hydrocortisone for periods ranging up to 28 months. One group received cortisone alone; the second group received cortisone followed by hydrocortisone; and the third group received hydrocortisone alone.

In the first group, the initial dose of cortisone varied from 100 mg. to 300 mg. per day, with several patients requiring as much as 500 mg. per day to control symptoms. This dosage was maintained for 1 to 2 weeks, then was reduced to a somewhat lower level for the next 2 or 3 weeks, and finally was gradually reduced to a maintenance level averaging 75 mg. per day for adults

and 40 mg. for children. When dosage was dropped below this maintenance level, symptoms recurred. All patients were kept on a limited salt intake and received potassium salts, anticholinergics to control pepsinogenesis and excessive gastric acidity, and anabolic agents (testosterone and Dienestrol). These adjuvants were gradually decreased as the dosage level of cortisone was reduced. The testosterone was given for its effect in reducing nitrogen loss, to help prevent adrenal atrophy, and to minimize loss of calcium and phosphorus. None of the patients in this series developed any of the more serious side effects often noted with long, continuous steroid therapy. There was some initial weight gain due to edema, and some secondary gain due to increased appetite. Of the 32 patients treated with cortisone alone, the results were excellent in 3, good in 18, fair in 8, and poor in 3.

Twenty-two of the 32 patients in the first group (cortisone-treated) were then given hydrocortisone. Each of these 22 patients had responded adequately to cortisone. The initial dosage of hydrocortisone was 20 per cent less than the current dosage of cortisone. Maintenance dosage averaged about 40 mg. per day for adults and 20 mg. per day for children, which was 40 per cent to 60 per cent of the maintenance dose of cortisone. In this group, the results were excellent in 6, good in 14, and fair in 2. All but 3 of the patients did better on hydrocortisone than on cortisone. One patient became edematous and 3 developed moon facies after transfer to hydrocortisone, but these complications disappeared when the dosage was reduced to maintenance levels.

The third series was comprised of 20 patients treated initially with hydrocortisone. Ten of these received no adjuvant treatment except for restriction of salt. The remainder were placed on salt restrictions and were given potassium salts until the dose of the steroid was below 80 mg. per day. The average initial dose was 200 mg. per day for 4 days, followed by 120 mg. per day for 3 days, 80 mg. for 3 to 7 days, and 60 mg. thereafter until the fourteenth day. After this time, dosage was gradually reduced to an average of 30 mg. to 40 mg. per day for maintenance. Results were observed to be excellent in 7 patients, good in 18, and fair in 5. Three patients showed transient mooning of the face, 2 had clinical edema, and 2 required anticholinergics to control ulcer pain. H. F.

ACTH Treatment of Asthma in Pulmonary Tuberculosis. Gregoire, F.: Canad. M. A. J. **74**: 146, 1956.

The case of a 20-year-old man with severe asthma and active tuberculosis who was treated with ACTH is discussed in detail. The tuberculosis had developed at age 18 and was confined to one apex. After 2 years of therapy with streptomycin and PAS, the patient still had a positive sputum. He had had asthma since the age of 3 years, and when he was free of asthma he usually had eczema. Following allergic investigation, he was treated with dust, ragweed, pyrethrum, and tree extract. The foods to which he showed positive responses were removed from his diet. At various times he had been given Vaponefrin, aminophylline, and antihistaminics, and he seemed to improve after hyposensitization therapy. Subsequently, he became critically ill with severe status. He was cyanotic and had obvious evidence of cor pulmonale. His sputum was still positive for tubercle bacilli, but, because of the severity of his asthma, he was started on ACTH, 20 units daily by the intravenous route. After 5 days, he received 20 units intramuscularly for 3 weeks. The dose was then reduced to 10 units daily intramuscularly and was maintained for the following year, at which time it was reduced to 5 units daily. In addition to the ACTH, the patient was kept on isoniazid therapy. His sputum has been

negative for a year. On the whole, his general condition improved markedly as evidenced by studies of the vital capacity, residual capacity, and the degree of air exchange in the lungs. Further evidence of improvement was noted in the arterial blood study findings.

The author concludes that "ACTH can be safely used in small doses for treatment of intractable asthma complicated by tuberculosis, if covered by antibiotics." He further implies that by markedly improving the patient's asthma, the ACTH may actually have helped to convert this patient's tuberculosis from an active to an inactive state. R. W.

Bronchial Asthma and Anaesthesia. Walton, F. A.: Canad. M. A. J. **74**: 624, 1956.

The author discusses the subject of the administration of anaesthesia to asthmatics. Patients were advised to stop smoking and to practice breathing exercises prior to surgery. Morphine was not used and atropine was favored over scopolamine because of its greater inhibiting effect on vagal reflexes and its less active drying action. When barbiturates were employed, only small doses were administered. Because of the possibility of sensitivity to rubber, endotracheal tubes made from a plastic material should be used. Sterile liquid petrolatum rather than water-soluble lubricants were recommended because the latter contain tragacanth. Curare, a respiratory depressant, was not used because it releases histamine and can cause or aggravate bronchial obstruction. Intravenous barbiturates and cyclopropane were avoided because of their parasympathetic stimulation and their action as respiratory depressants. Prostigmine was never employed. Dextran was avoided because of its potential allergenicity.

Patients in status asthmaticus were operated on under local or block anaesthesia. Abdominal cases were done by intercostal block and local infiltration, procaine or Xylocaine being used as the anaesthetics. Spinal anaesthesia was employed only if the level could be kept below the tenth thoracic segment so as not to interfere with intercostal or abdominal muscle action. For general anaesthesia, ether intravenously and by inhalation was employed as the anaesthetic of choice. The 4 to 5 per cent ether solution to be used for intravenous induction of anaesthesia was prepared by adding regular anaesthetic ether to 5 per cent dextrose in distilled water. The solution was allowed to run in rapidly so that the patient received somewhere between 7 and 16 c.c. of ether in approximately 15 minutes (140 to 320 c.c. of 5 per cent glucose solution). Occasionally, there was mild burning in the arm at the start of the drip but otherwise there was no unusual response. Small doses of Demerol (12 to 25 mg.) were added to the intravenous solution at 3-minute intervals to assist the induction. Once the patient was asleep, the anaesthesia was continued by inhalation ether or by nitrous oxide and oxygen. Gallamine (3 to 4 c.c.) was given initially for muscle relaxation and then was repeated in smaller doses when indicated. The author lists the following advantages for use of intravenous plus inhalation ether anaesthesia: "(1) controlled, measured administration; (2) anaesthesia not dependent on the rate or depth of respiration; (3) swift and quiet induction; (4) rarity of postoperative vomiting and pulmonary complications; (5) preservation of spontaneous respirations." There are no known disadvantages to this form of anaesthesia provided the 5 per cent concentration is not exceeded. The known beneficial effects which ether has upon the normal course of asthma was an additional reason for recommending its use.

In conclusion, the author strongly emphasizes the value of intravenous and inhalation ether anaesthesia in asthmatic patients requiring general anaesthesia and stresses the safety of this method of anaesthesia in such conditions.

R. W.

Dermatology

Nummular Eczema. Review of the Literature: Survey of 516 Case Records and Follow-up of 125 Patients. Weidman, A. I., and Sawicky, H. H.: Arch. Dermat. **73**: 58, 1956.

The case records of 516 patients with nummular eczema were reviewed, and 125 of these individuals were restudied. The cases were about equally divided between the sexes and the ages ranged from infancy to over 70 years. However, the condition occurred most frequently in the young and middle-aged groups. The duration of the lesions varied from a few days to 35 years. The dorsum of the fingers and hands and the exterior aspects of the forearms were the sites most commonly involved. The legs and thighs were less frequently involved, and the trunk and face were the least affected. Most of the patients experienced aggravation of the symptoms during the winter and were better in the summer. Patch tests made with potassium iodide and potassium bromide were usually positive. Since patients with numerous other dermatologic conditions also showed these positive patch test reactions, the response did not appear to be useful as a diagnostic criterion for nummular eczema. Only 11 per cent of the patients gave a positive personal history of atopy; 15 per cent gave a positive family history of allergy. Most of the patients were either housewives, manual workers, or factory workers, but the authors call attention to the fact that executives and professional people rarely attended their clinic for diagnosis or treatment. The most satisfactory therapeutic remedies were iodochlorhydroxyquin (Vioform) or tar preparations. Limited experience with hydrocortisone ointment indicated that this preparation was often very efficacious. The authors suggest that nummular eczema may not be a disease entity at all, but a symptom complex caused by multiple etiological factors, and that it does not appear to fit into one of the typical atopic diseases.

R. W.

The Effect of Non-Medicamentous Enclosure and "Dermatologic Rest" on Eczema. Simons, R. D. G. PH.: J. Invest. Dermat. **25**: 365, 1955.

Plastic bandages or splints were used to immobilize portions of the body in 103 patients with chronic eczematous dermatitis which had proved resistant to the usual methods of treatment. In some instances, joints were so splinted as to produce "surgical rest" of that extremity. The enclosure of eczematous skin with plastic bandage was termed "dermatologic rest." The scalp and face of children with facial eczema were plaster bandaged to resemble a helmet with open vizor. Despite this, contraction of the facial muscles made scratching possible. Immobilization was continued for a 2-week period in most cases. Non-immobilized, uncovered eczematous skin served as a control.

There were 90 adults and 13 children in the series. All of the latter had atopic eczema. The adult group showed chronic lichenified or pruriginous eczema of the hands, arms, and legs, or herpetoid eczema. Among the adults there were 12 cases of atopic eczema. After the first week of immobilization, a decrease in itching occurred. Marked improvement was obtained in 48 adults and 7 children. No beneficial effect occurred in 31 cases, and the lesions became worse in 19. Relapses occurred in 17 adults and 6 children, usually

after 2 weeks. The frequency of relapse was not considered greater than that obtained with other forms of therapy, including hospitalization. The high percentage of failure was attributed to the poor results obtained with weeping eczema lesions, most of which became secondarily infected following enclosure. Control skin sites remained unchanged except in 3 cases where a beneficial co-reaction ("Mitreaktion") occurred on the opposite untreated extremity. It was stressed that the plaster treatment was essenially a physical measure which allowed diseased skin to be put at rest. This treatment was not recommended as a routine measure, although striking results were obtained in a shorter time than that required for comparable results with other forms of therapy. M. C.

A Valuation of Hydrocortisone Ointment. Russell, B., Pegum, J. S., Thorne, N. A., and Grange, R. V.: Lancet **1**: 1038, 1955.

The authors treated 132 patients suffering from the following dermatologic conditions: anogenital pruritus, lichen simplex, infantile eczema, Besnier's prurigo, discoid eczema, chronic idiopathic eczematous dermatitis of the hands, otitis externa, and pruritic psoriasis. There were 12 patients with infantile eczema and 23 with discoid eczema in the group. The treatment materials studied were hydrocortisone ointment, in 1 per cent and 2.5 per cent concentrations, and the vehicle base which contained propylene glycol, polyethylene glycols, and zinc stearate. The ointments were dispensed weekly in 5 Gm. amounts in unlabeled tubes. Neither the doctor nor the patient knew which preparation the tube contained. Patients were furnished cards on which they were to record their daily progress.

Patients with discoid eczema experienced good results, but only a small number of cases of infantile eczema showed any improvement. The ointment base alone was found to be quite effective in many conditions, but the hydrocortisone ointment was clearly more effective than the vehicle base in discoid eczema. Only one patient developed a definite contact sensitivity to the vehicle base. R. W.

Chemical Changes at Site of Allergic Manifestation. Chatterji and Banerji: Bull. Calcutta School Trop. Med. **3**: 160, 1955.

A portion of skin from the site of an urticarial lesion was excised and extracted in hydrochloric acid solution. The histamine content of the extract was then measured. Skin from the site of a previous urticarial lesion no longer active was similarly treated and served as a comparison. Histamine was present in both extracts, but the extract of skin from the active lesion contained 3.5 times more histamine than that prepared from skin taken from the inactive site. A similar experiment performed with the skin of a patient with dermographism failed to show any histamine activity. The data reported support the theory that urticarial lesions are produced by a defect in the production of histaminase associated with the liberation of histamine at the site of the lesions. M. C.

Contact Photodermatitis. Sams, W. M.: Arch. Dermat. **73**: 142, 1956.

A papular eruption following the application of 2 sun-screening preparations and subsequent exposure to the sun is described in a 5-year-old child. The rash was limited, for the most part, to the exposed areas. The preparations used were Skolex and Neo-A-Fil cream. After the rash had cleared, the patient was patch tested with each material. Routine patch reactions were

negative, but when an erythema dose of ultraviolet light was applied over the tested sites, a definite sensitivity response was produced in the area covered by Neo-A-Fil cream.

In addition, the author studied a patient known to develop photosensitivity following the application of Shalimar perfume to the skin and the subsequent exposure to sunlight. A site was streaked with a 1:100 alcoholic dilution of Shalimar perfume and the following materials were placed across the streak before the area was exposed to an hour of moderate sunlight: (1) 3.5 per cent digalloyl trioleate in alcohol; (2) 5 per cent menthyl anthranilate (menthyl-O-aminobenzoate) in alcohol; (3) 1 per cent aqueous solution of quinacrine hydrochloride (Atabrine); (4) 1 per cent aqueous solution of chloroquine phosphate (Aralen). The 1 per cent solution of quinacrine hydrochloride and the 5 per cent solution of menthyl anthranilate blocked the sun's rays, while the 1 per cent chloroquine phosphate had no screening effect. In the area where the 3.5 per cent digalloyl trioleate solution was applied, as well as in the Shalimar streak, a sensitivity reaction of erythema and edema was manifest at the end of a 24-hour period. These responses subsided in about 7 days.

In a second experiment on the same patient, parallel streaks of a 3.5 per cent solution of digalloyl trioleate and Neo-A-Fil cream were made on an area of skin not previously exposed to sunlight (axilla). The sites were then exposed to sunlight for 1 hour. A first-degree erythema developed in the unprotected skin, but the screened areas were unaffected. At the end of 24 hours, the treated sites were still clear but, after 36 hours, itching and a papulo-urticarial eruption began at the edges of the screening streaks. These reactions subsided after 6 days. Control sites where the materials had been applied without sun exposure showed no reaction. The same experiment was repeated again, using only the 3.5 per cent alcoholic solution of digalloyl trioleate on the inner surface of the arm. A papular dermatitis developed in the treated area 72 hours following exposure to the sun. This reaction persisted for 3 days. Attempts to passively transfer the reactions of Shalimar perfume and 3.5 per cent digalloyl trioleate in the presence of sunlight by the usual technique on 4 different subjects were unsuccessful.

The author cautions that screening substances, such as digalloyl trioleate, used to prevent sunburn may induce a photosensitivity. R. W.

The Penetration and Distribution of C^{14}-Hydrocortisone in Human Skin After Its Topical Application. Scott, A., and Kalz, F.: J. Invest. Dermat. **26**: 149, 1956.

Radioactive hydrocortisone containing C^{14} was mixed with 1 per cent stable hydrocortisone ointment and applied to the skin of normal human volunteers, to hyperkeratotic skin, and to skin which had been treated with ultraviolet and Grenz irradiation. Biopsies of the treated areas were taken at intervals and radioautographs were made. In normal skin, radioactive material was visualized in the epidermis after 1 hour, was concentrated in the basal layer by 2 hours, was present in the cutis about the blood vessels after 6 hours, and had disappeared entirely from the skin after 16 hours. On hyperkeratotic skin, C^{14}-hydrocortisone failed to penetrate the epidermis by 2 hours but did so after 6 hours. Irradiated skin demonstrated a more rapid penetration of the tagged hormone before and during the early erythema than did normal skin, but there was no difference from normal during the late erythema. It was concluded that hydrocortisone applied to skin penetrates the epidermis and is concentrated temporarily in the basal layer. Penetration was found to be no greater from the hair follicles than from the rest of the epidermis.

M. C.

Miscellaneous Allergies

Plasmocytosis in Serum Sickness From Tetanus Antitoxin. Report of a Case. Carnig, P., and Hedrick, E.: Am. J. Clin. Path. **24**: 802, 1954.

A man who had previously received tetanus antitoxin without untoward reaction received, on March 13, penicillin and tetanus antitoxin for a puncture wound. On March 17, he developed chills, fever, nuchal tightness, and hemicranial pain, followed in 24 hours by urticaria and a morbilliform rash. He later developed pain with tenderness in the extremities. On March 21, differential count of the peripheral blood showed 17,200 white cells with 17 per cent plasmocytes, 2 per cent plasmocyte precursors, 2 per cent eosinophils, 6 per cent monocytes, 5 per cent lymphocytes, and 68 neutrophils. The sternal marrow study of the same date was remarkable for the presence of 23.5 per cent cells of the plasmocytic series. All globulin fractions of the serum were above normal limits. On March 25, 3 per cent of the 6,300 leucocytes in the peripheral blood were plasmocytes. E. K.

Histaminic Cephalgia: Differential Diagnosis and Treatment. Horton, B. T.: Proc. Staff Meet., Mayo Clin. **31**: 325, 1956.

Since 1937, the author studied 1,176 patients (1,023 men and 153 women) suffering from histaminic cephalgia. A provocative test consisting of the subcutaneous administration of 0.35 mg. of histamine base was performed on patients who had not been observed during spontaneous attacks. More than 60 per cent of the tested group developed typical histaminic cephalgia. A negative test, however, was not regarded as sufficient evidence to rule out the diagnosis of histaminic cephalgia. The author describes this type of headache as a "localized anaphylactoid reaction with both localized and systemic manifestations" caused by the release of histamine from sensitized cells.

Therapeutically, mild attacks were often controlled by breathing 100 per cent oxygen. Severe attacks frequently can be aborted by the intravenous administration of 1 c.c. of dihydroergotamine (D.H.E. 45) given soon after the onset of symptoms. Nocturnal attacks were frequently prevented by the use of rectal suppositories of ergotamine tartrate and caffeine at bedtime. Prophylactically, the management of histaminic cephalgia consisted of injecting gradually increasing doses of histamine subcutaneously at frequent intervals. M. C.

A Fatality Associated With Chlorpromazine (Largactil) Therapy. Theriault, J. C.: Canad. M. A. J. **74**: 148, 1956.

The author reports the case of a 38-year-old female patient who had been admitted to a mental hospital on several occasions for the treatment of schizophrenia. Because of her poor response to shock therapy, she was treated with chlorpromazine, 300 mg. daily. At this time, she received no medication other than the chlorpromazine. Within 2 weeks, there was remarkable improvement in her mental status. At this time, she developed an acute pharyngitis and a temperature of 103.8° F. She failed to respond to penicillin and streptomycin, her temperature remained elevated, and she was given Aureomycin. A blood count done 48 hours after the onset of her acute illness showed only 450 white blood cells. Otherwise, the blood picture was essentially normal. The blood smear showed only lymphocytes, and the cells were so difficult to find that a differential count could not be done. A bone marrow smear showed no granulocytes. After she became severely jaundiced and developed signs of kidney irritation, her condition deteriorated rapidly. She was given blood

transfusions, Aureomycin, and 100 mg. of cortisone, but she died 5 days after the diagnosis of agranulocytosis was established. The author stresses the importance of frequent blood studies on all patients taking chlorpromazine.

R. W.

Unique Allergic Response to Sulfisoxazole (Gantrisin). Report of a Case. Davis, J. B., and Tachdjian, M.: J. A. M. A. **161**: 228, 1956.

A 77-year-old woman was given sulfisoxazole therapy for a urinary tract infection. An initial dose of 1 Gm., followed by 0.5 Gm. twice daily, was administered. Three days later, a maculopapular rash developed on the back and the temperature rose to 103° F. On the following day, the entire body was covered by a severe bullous dermatitis. Also present were severe stomatitis and conjunctivitis, as well as periorbital, circumoral, and laryngeal edema. The temperature rose to 104° F., and the patient's condition was critical. After treatment with steroids and antibiotics, she showed marked improvement within several days.

M. C.

Anaphylaxis

The Mechanism of Arthus Reactions. I. The Role of Polymorphonuclear Leucocytes and Other Factors in Reversed Passive Arthus Reactions in Rabbits. Humphrey, J. H.: Brit. J. Exper. Path. **36**: 268, 1955.

Normal rabbits were injected intravenously with bovine serum albumin, hen ovalbumin, human gamma globulin, or pneumococcal polysaccharide. After one-half to one hour, the corresponding homologous antiserum was injected intracutaneously on each side of the animal's abdomen. The edema volume of the reversed passive Arthus (R. P. A.) reactions usually reached a maximum within 7 to 10 hours. The R. P. A. reactions were studied in animals at various intervals after treatment with nitrogen mustard. Four days after the nitrogen mustard was given, the polymorphonuclear leucocyte count approached zero. At this point the R. P. A. reactions were abolished. The size of the reactions paralleled the level of the polymorphonuclear leucocytes, but did not correlate with the mononuclear cell count.

To eliminate the possibility that nitrogen mustard abolished the R. P. A. reaction by some means other than by its effect on the polymorphonuclear leucocyte, the experiments were repeated with the abdominal aorta clamped for 5 minutes during and after the injection of mustard gas. In this way, the femoral bone marrow escaped the toxic effects of nitrogen mustard but the rest of the body was subjected to the drug. Although the neutrophil leucocyte count diminished, the reduction was not sufficient to inhibit the R. P. A. reaction. These studies demonstrated that nitrogen mustard did not inhibit the reaction by any direct effect on the skin sites. Platelet counts done after nitrogen mustard administration failed to reveal a sufficient reduction to explain the inhibition of the R. P. A. reaction. Serial studies of the histamine content of the washed buffy layer of blood failed to show significant changes. The effect of nitrogen mustard upon the reactivity of capillaries was studied by injecting a dye intravenously in nitrogen-mustard-treated rabbits and then measuring the diffusion of the dye at skin sites injected with histamine, leukotaxine, or histamine liberator 48/80. These local reactions showed no appreciable differences from those obtained in untreated animals. Thus, the effect of nitrogen mustard on Arthus reactions could not be explained by its effect on resistance to capillary-damaging agents. In one series of nitrogen-mustard-treated rabbits, an attempt was made to replace the neutrophilic leucocytes

by transfusion of cells obtained from peritoneal exudates. In only one instance could the circulating polymorphonuclear leucocyte level be raised by such transfusions, and in this animal the size of the R.P.A. reaction increased. In other neutrophilic-leucocyte-depleted animals, peritoneal exudates were injected intracutaneously with the antisera, and the R.P.A. reactions were partially restored. The changes in capillary permeability at the sites of R.P.A. reactions were studied by pretreatment with intravenous injections of dye. A blue area appeared at the site of antibody injection in one hour and reached its maximum intensity during the next 3 to 4 hours. The area of visible edema extended beyond the stained area. In nitrogen-mustard-treated animals, the diffusion of dye at the reaction sites was almost completely inhibited. Heparin, given in large doses, reduced the size of the R.P.A. reactions, but failed to inhibit them or to change their appearance. R.P.A. reactions were induced in areas which were previously denervated. The reactions were more rapid and severe in the denervated areas than in control areas, probably due to the increased blood flow as a result of the operative procedure.

On the basis of the results of the above experiments, plus histologic studies reported herein, the author suggests that the sequence of events in the reversed passive Arthus reaction occurs as follows:

Stage I. A slowly developing, but minor, damage to the local blood vessels results from the union of antigen with antibody at the site which causes stickiness of the endothelium and arteriolar spasm. A transient increase in capillary permeability coincides with the onset of endothelial stickiness.

Stage II. Adherence of neutrophilic leucocytes to the vessel walls is noted and intravascular clumping of leucocytes and platelets occurs. Histamine and 5-hydroxytryptamine are probably released in appreciable amounts from the platelets, causing further increase in arteriolar spasm and in capillary permeability. As the reaction continues, more polymorphs accumulate, more cellular thrombi are formed in the vessels, and destruction of vessel walls occurs. The polymorphs also migrate into surrounding tissues and gross edema becomes apparent. The changes of this stage are abolished by treatment with nitrogen mustard when the circulating polymorphonuclear leucocyte count is drastically lowered. This indicates that the accumulation of polymorphs is essential for the vascular destruction and edema, which are the main features of severe reactions. Platelets are not essential for the destructive phase of the reaction, although the histamine and 5-hydroxytryptamine released by them may be important in causing spasm and endothelial stickiness. Stage II reaches its height in 6 to 12 hours and is gradually replaced by Stage III.

Stage III. The reaction site is invaded by macrophages and there is a local proliferation of histiocytes. This is accompanied by degeneration and disappearance of polymorphonuclear leucocytes, removal of leucocyte-platelet thrombi, and by repair of vascular damage by proliferation of endothelial cells. The presence of neutrophilic leucocytes is not essential to this stage and thus this stage is not affected by nitrogen mustard. B. S.

The Mechanism of Arthus Reactions. II. The Role of Polymorphonuclear Leucocytes and Platelets in Reversed Passive Reactions in the Guinea Pig. Humphrey, J. H.: Brit. J. Exper. Path. **36**: 283, 1955.

The technique of producing reversed passive Arthus (R.P.A.) reactions in the guinea pig was similar to that employed in the rabbit. One difference was the use of heterologous (rabbit) antisera because sufficient precipitating

antibody could not be produced in the guinea pig. Furthermore, the effect of nitrogen mustard on leucocytes and R.P.A. reactions could not be studied because this agent proved to be too toxic for the guinea pig. To overcome the first difficulty, antisera were prepared in rabbits against guinea pig polymorphs and platelets. An intraperitoneal injection of this rabbit anti-neutrophil serum into the guinea pig caused a rapid reduction in neutrophils to 0 to 1 per cent, and this effect persisted for five days. The peripheral neutropenia was accompanied by similar changes in the bone marrow. Other formed elements of the blood remained unaffected, with the exception that lymphocytes tended to suffer some reduction.

R.P.A. reactions were performed in guinea pigs which had received the antineutrophil serum intraperitoneally two days previously and in a control group of animals which had received normal rabbit globulins. The edema volumes at the sites of the R.P.A. were much smaller in the neutrophil-depleted guinea pigs than in the control animals. There was no difference in the response of depleted and control animals to the intracutaneous injection of histamine, histamine liberator 48/80, and leukotaxine, demonstrating that capillary permeability did not vary in the two groups.

In another experiment, guinea pigs were sensitized passively with rabbit antibody to pneumococcal capsular polysaccharide and at the same time received antineutrophil or normal rabbit globulins. Two days later, they were injected intravenously with dye and intracutaneously with the polysaccharide antigen. The blueing at the injection sites was rapid and equal in area and intensity in depleted and control animals, again demonstrating that depletion of neutrophils does not alter capillary permeability.

Guinea pigs injected with rabbit antiplatelet antibody globulins showed a reduction in platelets to 20,000 per cubic millimeter or lower in 24 hours. This reaction persisted for about 5 days, during which time petechial hemorrhages appeared and some animals died. These platelet-depleted and normal control animals were subjected to R.P.A. reactions. Strict comparison of reactions was difficult because of the state of the treated animals, but the edema of the reactions appeared to be greater in the platelet-depleted animals than in the controls.

Skin sites were biopsied at various intervals after the onset of R.P.A. reactions in normal and in neutrophil-depleted guinea pigs and then studied histologically. The general picture of edema, vascular necrosis and thrombosis, and perivascular infiltration by polymorphs and mononuclear cells was similar in both groups of animals. However, in polymorph-depleted animals, vascular necrosis and edema were much less marked despite a pronounced mononuclear cell accumulation.

Thus, the course of R.P.A. reactions in guinea pigs and rabbits and the effect of polymorph depletion on these reactions are similar. In both groups of animals, the depletion was achieved by different mechanisms, which added weight to the conclusion that the absence of polymorphs, rather than other factors, was responsible for the diminution of edema and the decrease in vascular damage observed in depleted animals. Conversely, polymorph accumulation is a major factor in the R.P.A. reaction and is responsible for damage to the capillary walls and for blocking the lymphatics in the second stage of the reaction. B. S.

Pharmacology, Physiology, and Pathology

Effect of Cortisone on the Reticulo-Endothelial System. Nicol, T., and Snell, R. S.: Nature **177**: 430, 1956.

Seventy-nine guinea pigs were given daily injections of trypan blue subcutaneously for 6 days prior to being killed by chloroform. Seven of the

animals were used as controls. The remaining animals were divided into groups and given, in addition to the dye, 5, 10, or 25 mg. of cortisone intramuscularly once daily for a period of 1, 2, 3, or 4 weeks. The activity of the reticulo-endothelial system in the spleen, liver, and lymph nodes was assessed by the number of dye-bearing cells present and the intensity of the vital staining in fixed stained sections. In the animals that received cortisone for 1 or 2 weeks, the intensity of vital staining in the macrophages was markedly reduced, their mortality was high, and the lymph nodes became atrophied. These effects appeared earlier in the animals that received higher doses of cortisone. Post-mortem examination of the guinea pigs which succumbed suggested that death had occurred as a result of the reticulo-endothelial system being depressed and unable to detoxicate the trypan blue. In the animals that received cortisone for 3 or 4 weeks, the vital staining was practically identical to that of the controls, the mortality was low, and the lymph nodes were hypertrophied. The experiments suggest that patients should be especially protected from intercurrent infections during the early stages of cortisone treatment. I. G.

Effect of Cortisone on the Blood. Nicol, T., and Bilbey, D. L. J.: Nature **177**: 524, 1956.

The cardiac blood of 12 guinea pigs receiving daily intramuscular injections of 10 mg. of cortisone acetate was examined weekly for 5 weeks. During the first two weeks of treatment the degree of polychromasia and anisocytosis seen in the normal blood picture increased, and at the end of the second week immature red cells were present in greater numbers. No significant change was noted in the red cell count, but there was a slight drop in the hemoglobin. The total leucocyte count dropped below normal during the first three weeks and then rose above normal during the fourth and fifth weeks of treatment. These changes were accounted for by a sustained fall in the number of lymphocytes and a gradual rise after the first week in the number of pseudoeosinophils. When the pseudoeosinophil count dropped at the end of the first week, a high proportion of the cells showed multiple nuclear lobes, whereas from the second to the fifth week, as the pseudoeosinophils increased in number, a greater proportion showed a single lobe, indicating increased production of polymorphs. I. G.

Studies of 17-Hydroxycorticosteroids. V. Responses of 17-Hydroxycorticosteroids, Eosinophils, and Glucose to ACTH and Epinephrine. Ely, R. S., Bray, P. F., Raile, B., and Kelley, V. C.: J. Clin. Invest. **33**: 1587, 1954.

The blood responses of normal and abnormal children to injected corticosteroids, ACTH, and epinephrine were studied. Six children with congenital adrenal hyperplasia showed higher eosinophil counts and lower glucose and 17-OH-corticosteroid levels than 40 normal children. The eosinophil response to ACTH in children with congenital adrenal hyperplasia was less than normal, although their response to epinephrine was normal. In this group, ACTH produced no elevation of 17-OH-corticosteroid levels. Epinephrine failed to change plasma 17-OH-corticosteroid levels in any of the 51 children so tested. The glucose response to epinephrine was considerably greater than that to ACTH in all groups of children. Glucose responses did not correlate with eosinopenic responses when either epinephrine or ACTH was used as the eliciting agent.

Since eosinophil response to epinephrine occurred in the absence of demonstrable increase in plasma 17-OH-corticosteroid levels, it is suggested that there is no quantitative relationship between these two reactions. It is

concluded that the epinephrine-induced eosinophil response is not a valid criterion of adrenal cortical function. No significant correlation was found between responses of glucose, eosinophils, and 17-OH-corticosteroids to ACTH. Of these 3 tests, the 17-OH-corticosteroid response to ACTH is considered the most valid measure of adrenal function; the eosinophil response to ACTH still has clinical value as a screening test. E. K.

Inhibition of the Local Shwartzman Reaction by Dicumarol. Spanoudis, S., Eichbaum, F., and Rosenfeld, G.: J. Immunol. **75**: 167, 1955.

Seven normal rabbits were sensitized intracutaneously and 24 hours later were injected intravenously with a provocative dose of *S. marcescens* toxin. The hemorrhagic lesions of the local Shwartzman reaction were fully developed about 120 minutes after the intravenous injection. Five other rabbits were treated with daily oral doses of Dicumarol for 4 days in sufficient dosage to lower the prothrombin time level below 1 per cent. On the fifth and sixth days, respectively, the sensitizing and provoking injections of toxin were administered. These animals failed to demonstrate a positive local Shwartzman reaction. Platelet counts were performed in both groups of rabbits before each injection and 15, 30, 60, and 120 minutes after the provoking injection. In both groups, the sensitizing injection produced a similar moderate drop of platelets as measured at 24 hours and a pronounced diminution 15 to 30 minutes after the provoking injection. The latter effect was also noted in one rabbit which had been injected intravenously with toxin only. Thus, the thrombocytopenia following the toxin injections depends on the direct action of the toxin, there being no correlation with the presence or absence of the Shwartzman reaction. The results of these studies with Dicumarol confirm the results of previous studies with heparin. It is apparent that the interference with blood coagulation produced by these two drugs, which have different modes of action, is the essential factor responsible for the inhibition of the local Shwartzman reaction. B. S.

Miscellaneous

Immunochemical Studies of Antitoxin Produced in Normal and Allergic Individuals Hyperimmunized With Diphtheria Toxoid. IV. Differences Between Human Precipitating and Non-Precipitating Skin-Sensitizing Diphtheria Antitoxin as Shown by Electrophoresis. Kuhns, W. J.: J. Exper. Med. **99**: 577, 1954.

Diphtheria toxoid elicits precipitating antitoxin and a nonprecipitating skin-sensitizing antitoxin which is closely similar to the atopic reagin. Human subjects were bled 7 to 19 days after receiving a diphtheria toxoid booster injection and electrophoretic studies of their sera were carried out in a starch-supporting medium. The starch block was then cut into segments to separate the serum fractions. The antitoxic activity of these segments was tested intracutaneously in rabbits, by precipitin examination, and by passive transfer in human Shick-positive recipients. Skin-sensitizing antitoxin was concentrated in the faster-moving part of the gamma globulin fraction, and precipitating antibody was found in a slower-moving part of the gamma globulin fraction. The fast-migrating gamma globulin was equivalent to whole serum in its skin-sensitizing ability. The migration of skin-sensitizing antitoxin was "such that demonstrable antitoxic activity occurred over a considerable range of the gamma globulin and portions of the beta globulin. . . ." Fractionated

sera from two individuals who formed only nonprecipitating antitoxin in response to diphtheria toxoid were used to sensitize skin of human recipients. As little as .01 unit of antitoxin sensitized human sites so that a subsequent test with 0.1 Lf toxoid in 0.02 c.c. volume elicited a greater wheal at the test site than at the control site. One of these sera exhibited the same properties 20 months after hyperimmunization with toxoid. Precipitating antitoxin did not exhibit cutaneous passive transfer sensitization. In 2 sera skin-sensitizing antitoxin occurred alone, and in 4 sera precipitating antitoxin occurred alone. In 3 instances both types of antitoxin were found, each type representing part of the total serum antitoxic activity. Certain sera were found capable of inhibiting wheal reactions in appropriately prepared recipients. ". . . It is possible that previous differences in skin activity in fractions from allergic sera separated by electrophoresis may have been due in part to the presence of varying amounts of blocking antibody." E. K.

Immunochemical Studies of Antitoxin Produced in Normal and Allergic Individuals Hyperimmunized With Diphtheria Toxoid. V. Peculiar Electrophoretic Configuration of Serum Proteins and Protein-Bound Polysaccharides in Certain Antitoxic Sera. Demonstration of Serum Changes in Certain Severe Manifestations of Allergy. Kuhns, W. J.: J. Exper. Med. **100**: 485, 1954.

In the course of repeated electrophoretic fractionations of sera from human beings hyperimmunized with diphtheria toxoid, it was noted that the beta globulin peak was large as compared with the $alpha_2$ globulin peak in those sera containing skin-sensitizing antitoxin. In sera containing precipitating antitoxin, the converse was true. Paper electrophoresis was carried out before and after the administration of a booster dose of diphtheria toxoid. The patterns observed are described in detail. The electrophoretic pattern of antitoxic sera containing only precipitating antitoxin was that of normal nonimmune serum. Skin-sensitizing sera showed a relatively large beta globulin and a small $alpha_2$ globulin component. Serum bound polysaccharides migrated more slowly in skin-sensitizing serum than in sera containing precipitating antitoxin. No demonstrable differences were noted in sera taken before and after the administration of toxoid.

One untreated and one hyposensitized subject with hay fever showed no unusual electrophoretic patterns. A third subject with hay fever showed slight changes in his $alpha_2$ and beta globulins on exposure to chymotrypsin which induced clinical hay fever symptoms. Eosinophilia, due in one case to penicillin sensitivity and in another instance to unknown causes, was associated with serum electrophoretic characteristics observed in high-titred skin-sensitizing antitoxic sera. There were distinctive changes in subjects having active rheumatic fever. E. K.

Disseminate Endarteritis. Report of a Case. McLetchie, N. G. B., and Gillis, D. A.: Am. J. Clin. Path. **25**: 502, 1955.

The case of a 44-year-old man who was ill for 2 months with pain in the legs and hands is reported. He became febrile, developed marked muscular wasting and weakness, enlargement of the liver, ankle edema, leucocytosis of 15,000 to 20,000 without eosinophilia, increased serum globulin, transient hypertension, and left ventricular enlargement. He died 3 months after the onset of his illness. Autopsy disclosed cardiac failure and generalized wasting. Arterial changes were most significant and are described in detail. There

was a generalized endarteritis with fibroplastic intimal thickening obscuring the endothelium, hypertrophy and edema of the media, and increased vascularization of the adventitia. Organization of the lesion then led to a very vascular and thickened intima and progressive elastosis. It is suggested that "the condition in many ways represents a morphologic linkage between Buerger's disease and the vascular lesions of the collagen diseases." No mention is made of the patient's smoking habits. E. K.

Thrombotic Thrombocytopenic Purpura. Report of a Case With Discussion of Its Tinctorial Features. Fisher, E. R., and Creed, D. L.: Am. J. Clin. Path. **25**: 620, 1955.

A 22-year-old white man was hospitalized for muscular fibrillations which had appeared sporadically for many months. No organic cause was found. Two years later a blood eosinophilia of 40 per cent was noted. He also had an unproductive cough. An allergic investigation, including skin tests and parasite studies, gave negative findings. At the age of 25 years, anemia and leucocytosis of 25,000 were recorded. Bone marrow studies revealed granulocytic hyperplasia especially of eosinophils. When the patient was 30 years of age, he developed purpura, frontal headache, dizzy spells and diplopia, and was hospitalized. He was found to have anemia with a leucocytosis of 24,000, 70 per cent eosinophils, and 30,000 platelets per cubic millimeter. Paper electrophoresis disclosed "an increased gamma globulin, decreased beta globulin and a prominent alpha$_1$ globulin." He died in uremia 3 months after hospitalization. Adrenal steroids did not affect the course of his illness. The pathologic picture of thrombotic thrombocytopenic purpura was found at autopsy. It is suggested that hypersensitivity may have been a significant pathogenetic factor in this case. E. K.

Immunologic Studies in the Lymphoblastomas. II. The Ability to Develop an Eczematous Sensitization to a Simple Chemical and the Ability to Accept Passive Transfer Antibody. Rostenberg, A., Jr., McCraney, H. C., and Bluefarb, S. M.: J. Invest. Dermat. **26**: 209, 1956.

An attempt was made to sensitize a group of patients having lymphoblastomatous diseases to 2:4 dinitrochlorobenzene by applying the chemical to the volar surface of the patient's arm and allowing it to evaporate. After approximately 3 weeks, another area of skin was challenged with the chemical. Only 1 of the 31 patients treated in this manner developed eczematous sensitization, and this patient exhibited a spontaneous "flare-up" phenomenon. The control group consisted of 14 hospitalized patients with other ailments. Three of these became sensitized. In a second experiment, 10 "lymphoma-leukemia" patients were passively sensitized with 2 human sera known to contain antibodies either against guinea pig serum or against ragweed protein extract. Positive passive transfer reactions were obtained in each case when the sites were tested with the antigen. The impaired ability of patients with lymphomatous diseases to develop allergic eczematous sensitization to simple chemicals was attributed to a specific effect of the disease process on cells of the lymphoreticular system. M. C.

Craniovascular Studies in Headache: A Report and Analysis of Pulse Volume Tracings. Brazil, P., and Friedman, A. P.: Neurology **6**: 96, 1956.

Direct measurements of pulsation were obtained by electrical recordings made from the volume changes in the temporal, occipital, and supraorbital

arteries in 188 patients with migraine and in 103 patients with tension or muscular contraction headache. The changes in pulsations and subjective responses were observed and recorded before and after the administration of dihydroergotamine, nicotinic acid, or sterile water. There were 76 patients with migraine who were given dihydroergotamine, and 69 of these showed diminished volume pulse amplitudes along with relief from headache. Of 42 patients with tension headache, 33 obtained complete or partial relief of their headaches after receiving nicotinic acid and showed pulse-wave changes of increased amplitude. Symptomatic relief occurred before a change in the pulse volume tracings was apparent. M. C.

The Effect of Salm. Typhi and Its Endotoxin on the Phagocytic Activity of the Reticulo-Endothelial System in Mice. Biozzi, G., Benacerraf, B., and Halpern, B. N.: Brit. J. Exper. Path. **36**: 226, 1955.

The method of studying the activity of the reticulo-endothelial system (R. E. S.) of mice consisted of blood clearance measurements of carbon administered intravenously. When all the carbon had been cleared from the blood, the animals were sacrificed and the spleen and liver were weighed and studied histologically. A group of mice was given a sublethal intravenous injection of killed typhoid bacilli. A portion of this group was studied for activity of the R.E.S. within several hours to two days after the injection. The remaining animals in the group were given a second intravenous injection of killed typhoid bacilli 48 hours after the first injection, and part of this group was studied for activity of the R.E.S. The remaining animals received a last dose of bacteria on the fourth day after the initial injection, and the activity of the R.E.S. was studied at varying intervals after the injection. The activity of the R.E.S. in each series was compared to that of untreated control mice. The action of the initial injection of bacteria was a depressing effect on the phagocytic activity of the R.E. cells of the liver and spleen. It reached its maximum within 10 hours after the injection and persisted for 24 hours. The second dose of bacteria produced a marked stimulation of the phagocytic activity of the R.E.S., with an increase in weight of both the liver and spleen, possibly due to an increase in R.E. cells. The third dose of bacteria caused no further increase in phagocytosis. Following the fourth day after the initial injection, phagocytosis gradually decreased, and returned to normal on the ninth day. At this time, a relative hypertrophy of the liver and spleen was still evident. A similar series of experiments was performed with Boivin endotoxin prepared from typhoid bacilli. Again the initial intravenous injection of endotoxin decreased the phagocytic activity of the R.E.S. A subsequent injection of a larger dose of endotoxin caused a stimulation of the phagocytic activity of the R.E.S. The effects with endotoxin were found to be less intense than those obtained with killed bacilli. However, the results of these experiments indicated that the effect of the whole bacilli on the R.E.S. can be attributed to the endotoxin complex. Further studies with the polysaccharide extracted from the endotoxin showed that this fraction is not responsible for the action of endotoxin on the R.E.S.

Another series of mice was injected subcutaneously, either once, twice, or three times with killed typhoid bacilli. The phagocytic activity of the R.E.S. was investigated at varying intervals after the injections and compared to that of normal untreated animals. The subcutaneous route of administration of the bacilli caused an increase in phagocytic activity which was evident even after the first injection.

The initial studies with intravenous doses of bacilli were repeated, but one group of animals in this experiment was also given cortisone and one group of animals was given cortisone alone. The cortisone partially inhibited the stimulating effect of repeated doses of typhoid bacilli on phagocytic activity. The inhibitory effect of cortisone alone was not striking.

The authors believe that the difference in the effect on phagocytosis between the first and second intravenous injections of bacilli or endotoxin is due to increased tolerance or resistance of the R. E. cells after the second injection. The change, occurring in 48 hours, appears too early to be explained on the basis of immunity. These studies demonstrate the role of the R.E.S. in the defense of the animal against endotoxins of Gram-negative bacilli. B. S.

Malaria Immunity in African Negroes. Experimental, Epidemiological and Statistical Aspects. Gallais, P., and Collomb, H.: Presse méd. **64**: 161, 1956.

Therapeutic malarial infestations were induced in Europeans and in 19 Negro patients (17 Africans, 1 Martiniquan, and 1 Malagache) affected with syphilis of the central nervous system. None of the African Negroes was sensitive to the inoculation. Observations were carried out on military contingents from different parts of French territories, stationed in a hyperendemic area in the Far East and living under similar conditions. The resistance of the African Negroes to malarial infestation was remarkable, while the Europeans, Vietnamese, and North Africans were affected if the suppressive treatment was insufficient or irregular. Similar findings were noted in soldiers liberated from prisoners' camps in hyperendemic areas. The authors state that splenomegaly in adult African Negroes was never due to malaria. In a large military hospital in Marseille, receiving patients from all overseas French territories, not a single case of malaria was seen in nearly 4,000 admissions of African Negroes over a 5-year period. The nature and origin of the natural resistance of the African Negro to malaria is discussed. I. G.